Multiscale Modeling of Blood Flow and Platelet Mediated Thrombosis

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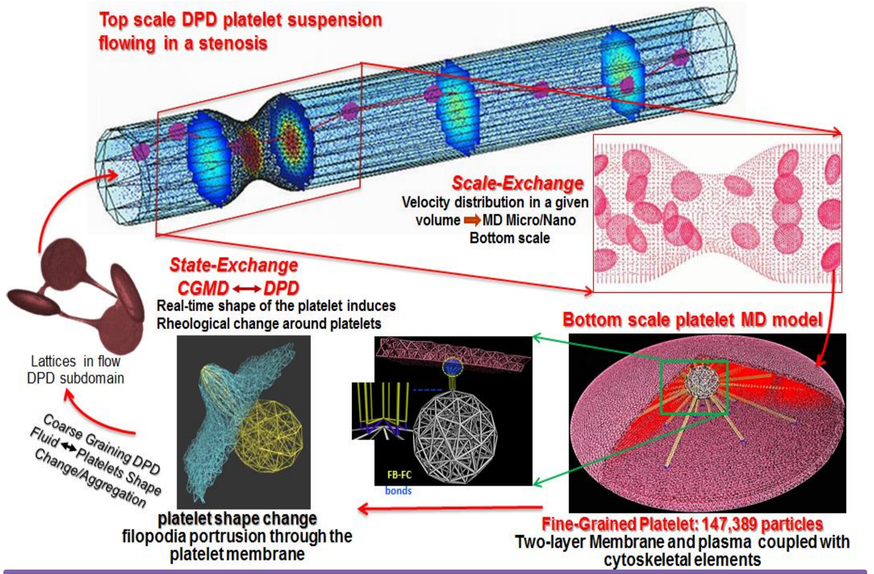
Project Summary

INTRODUCTION: We previously developed sophisticated particle-based methods, incorporating dissipative particle dynamics (DPD) and coarse-grained molecular dynamics (CGMD), to describe blood flow in cardiovascular pathologies and ensuing mechanotransduction events that may induce initiation of thrombosis via flow-induced platelet activation. This multiscale modeling (MSM) approach circumvents inherent limitations of continuum-based methods to cover the vast range of spatio-temporal scales required to describe the complex phenomena of flow-induced thrombosis. This model is tightly coupled to extensive *in vitro* measurements of platelet mechanical properties, shape change, and motion under flow. We have now improved our model to describe platelet recruitment in early shear-induced aggregation. [1-5]



MULTISCALE MODEL: Two Spatial-Temporal scale methods: [1]

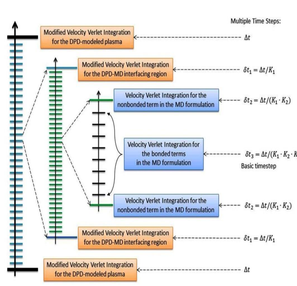
(1) Top/microscale using **D**issipative **P**article **D**ynamics (**DPD**) to describe viscous blood fluid flows (viscosity, compressibility);

(2) Bottom/nanoscale using **C**oarse **G**rained **M**olecular **D**ynamics (**CGMD**) to describe the platelet membrane, cytoplasm and the cytoskeleton.

ALGORITHMS FOR HPC: More Efficient Algorithms on HPC Resources:

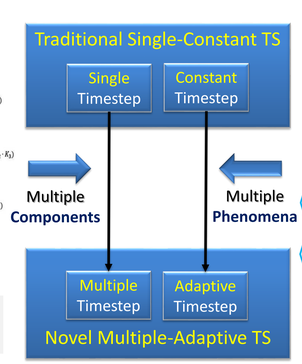
(1) Simulation Size:
- Platelet model: 140K particles, 8.38 μm³, ρ = 16,708/μm³
- Flow model: 10,787,776 particles, 20K μm³, ρ = 532/μm³
- Total: Flow 10.8M (97%) + 2×Platelets 280K (3%) = **11 Million Particles**

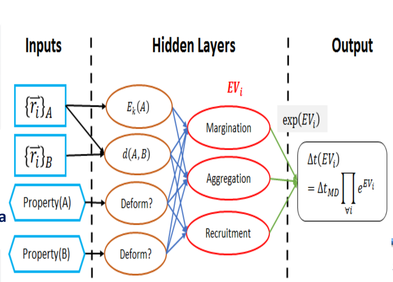
(2) Time Stepping Algorithms: MATS Framework for MSM
- Multiple Time Stepping (**MTS**) Algorithm: **Four-Level** Integrator
- Adaptive Time Stepping (**ATS**) Algorithm: **Event-Driven** Integrator



Multiple Time Stepping (MTS) algorithm

4-level integrator Jump factors: K_1, K_2, K_3





Adaptive Time Stepping (ATS) algorithm

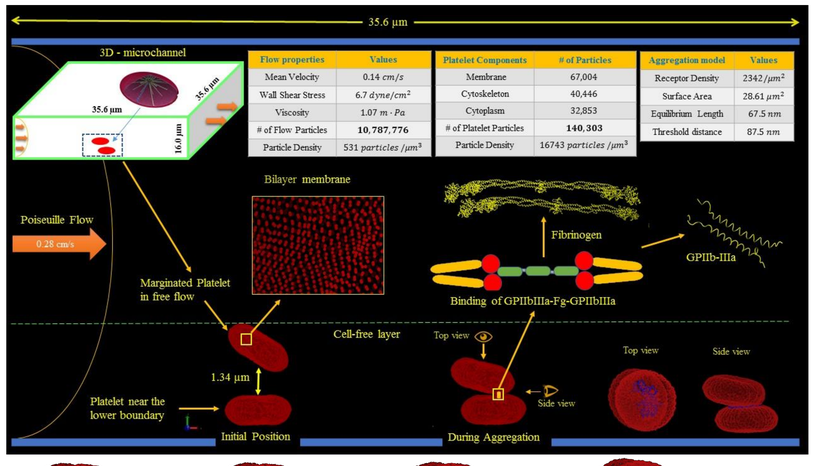
Event-driven timestep selection

Covered Spatial-Temporal Scales: Length: *nm – mm* **Time:** *ps – ms*

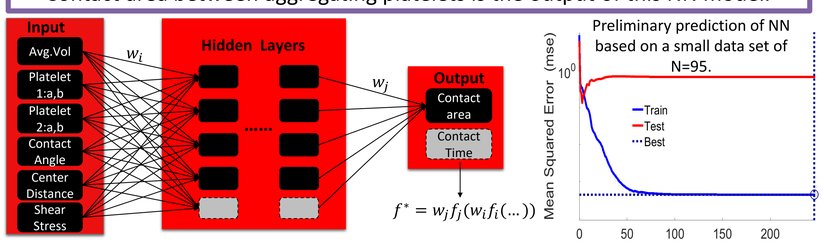
Progress and Milestones

➢ **Platelet Recruitment and Aggregation:** We construct a molecular-level hybrid force field that combines Morse and Hooke potentials to mimic the binding of **GPIIb-IIIa (αIIbβ3) receptor** and **Fibrinogen** during recruitment aggregation. The pairwise nonbonded interaction of the receptors is derived from the Morse potential and the bonded interaction is described as a harmonic function. The hybrid force field is parametrized for reproducing morphologic characteristic as contact area at aggregation through correlating with in vitro results.

$$U_{aggregation}(\boldsymbol{r}) = \sum_{bonds} \frac{f^A}{2r_0}(r - r_0)^2 + \sum_{neighbors} D_0\left(e^{-2\alpha(r-r_0)} - 2e^{-\alpha(r-r_0)}\right)$$

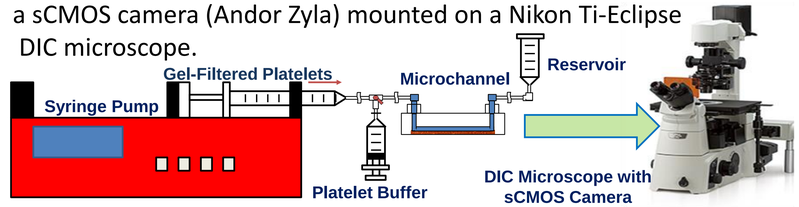


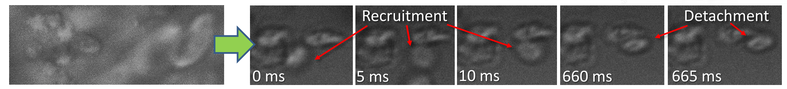
➢ **Prediction Model Using Machine Learning:** Experimental results are used to train a 2-layer, 10-node feedforward neural network (NN) model. Contact area between aggregating platelets is the output of this NN model.



➢ **Platelet Recruitment and Aggregation:** Experimental Validation

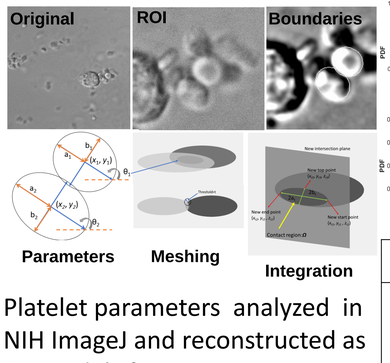
Gel-filtered platelets mixed with 1.5 mg/ml fibrinogen are perfused through 100 × 1000 μm microchannels with platelets adhered to von Willebrand factor at shear stresses 1-10 dyne/cm². Recruitment and aggregation events are recorded at 100× zoom and 420 fps with a sCMOS camera (Andor Zyla) mounted on a Nikon Ti-Eclipse DIC microscope.

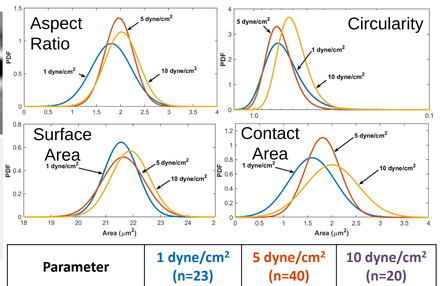




Margination/adhesion with red blood cells

Aggregation under flow conditions



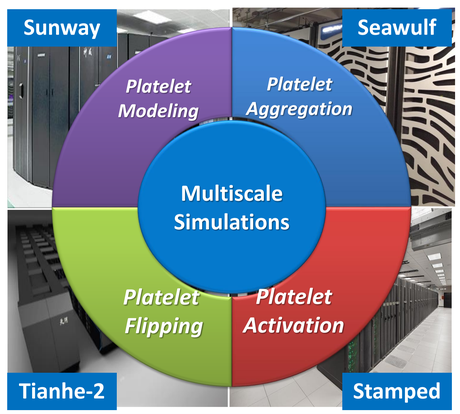


Platelet parameters analyzed in NIH ImageJ and reconstructed as 3D models for contact areas.

Parameter	1 dyne/cm² (n=23)	5 dyne/cm² (n=40)	10 dyne/cm² (n=20)
Aspect ratio	1.81 ± 0.42	1.97 ± 0.30	2.02 ± 0.35
Circularity	0.73 ± 0.15	0.74 ± 0.12	0.63 ± 0.11
Surface Area (μm²)	21.56 ± 0.62	21.64 ± 0.77	21.89 ± 0.7
Contact Area (μm²)	1.59 ± 0.48	1.81 ± 0.36	2.00 ± 0.55

➢ **High Performance Computing (HPC) Resources:** [2] [3].

- Stony Brook Seawulf & LI-Red Cluster (1 M core-hours)
- XSEDE SDSC Comet Supercomputer (2.5M core-hours)
- XSEDE TACC Stampede Supercomputer (120K core-hours)
- China's Tianhe-2 Supercomputer (110M core-hours)
- China's Sunway Supercomputer (3M core-hours)
- Total of Core-Hours: **120+** Millions on World's Top Supercomputers in United States and China



CONCLUSIONS: : Our multiscale numerical approach offers a computationally affordable, highly resolved, and validated method for modeling platelet activation, aggregation, and adhesion in shear flow. Biophysical properties of deformable platelets are accurately described down to the nanoscales, with hemodynamic stresses mapped on membrane and intra-platelet components. Ongoing simulations and experiments incorporate GPIb-vWF for aggregation at high shear stresses. Our models can be used to test development of new anti-platelet therapeutic approaches, such as novel lipid moieties that modulate platelet membrane and other biophysical properties to make the platelet more shear resistant. We are utilizing MSM to analyze the impact of clinically relevant shear forces generated via a range of devices and pathologies to predict cellular responsiveness driving thrombosis.

BioFluids Lab @ Stony Brook U

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- **XSEDE** (**DMS140019** on TACC Stampede, Zhang, Peng)
- **XSEDE** (**DMS150011** on SDSC Comet, Zhang, Peng)

PUBLICATIONS:

[1] Zhang, P., et al, *Cellular and Molecular Bioengineering*, 7:552-574, 2014.
[2] Zhang, P., et al, *Journal of Computational Physics*, 284:668-686, 2015.
[3] Zhang, P., et al, *Computer Physics Communications*, 204:132-140, 2016.
[4] Zhang, P., et al, *Journal of Biomechanics*, 50:26-33, 2017.
[5] Gao, C., et al, *Journal of Computational Physics*, 335:812-827, 2017.